ALIMENTAZIONE E VITAMINA D

Roma – Hotel Mediterraneo - 2 dicembre 2022

III° Modulo formativo

Modalità di supplementazione con vitamina D

La supplementazione di Vit. D nel paziente diabetico

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Vitamin D Supplementation in Diabetes

- Effects of vitamin D on glucose tolerance
- Vitamin D levels and type 2 diabetes
- Vitamin D supplementation in diabetes
  - Prevention of diabetes
  - Gluco-metabolic effects
  - Skeletal effects

Vitamin D Supplementation in Diabetes

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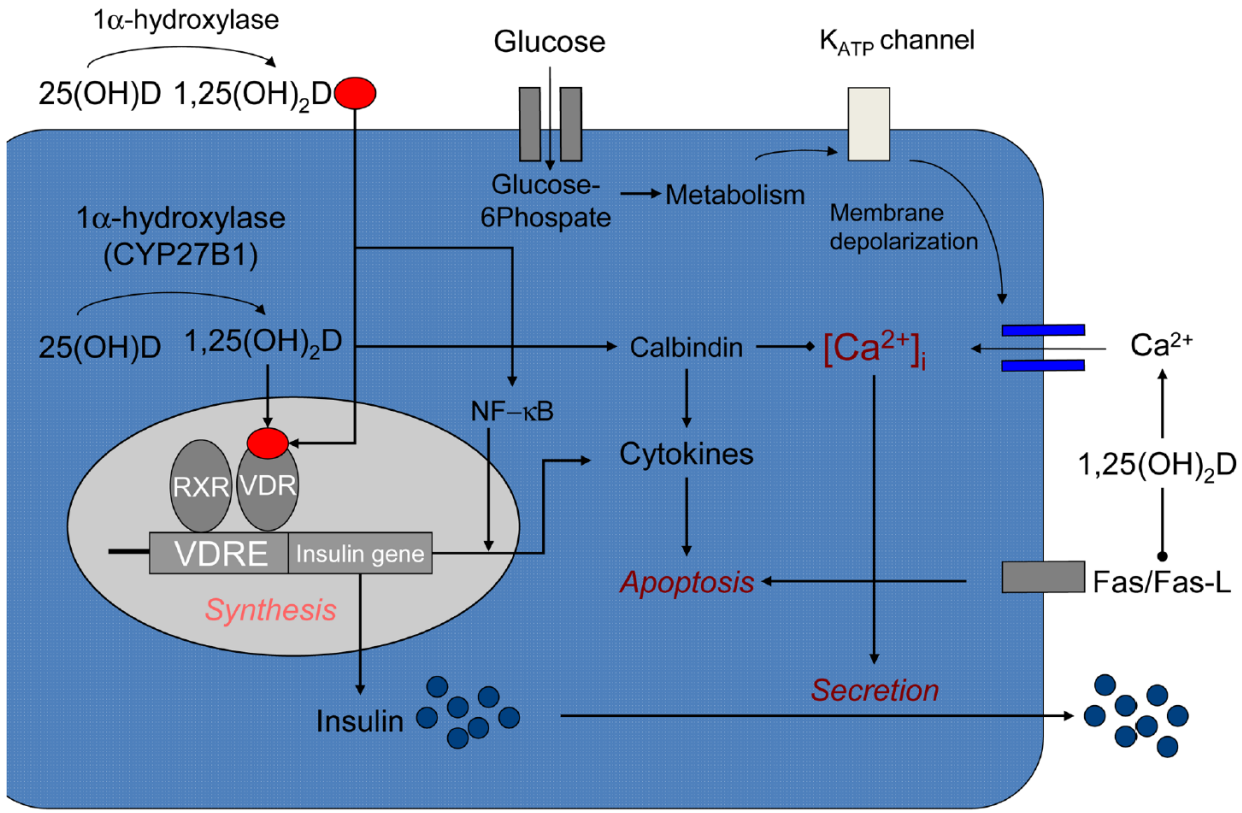
Vitamin D and Insulin Secretion

- The **1,25OH2D-VDR complex** binds to the **VDRE in the human insulin gene promoter**, to enhance the transcriptional activation of the insulin gene and increase the synthesis of insulin.

- Vitamin D may **promote beta-cell survival by** modulating the generation and effects of cytokines and by downregulating the Fas related pathways (Fas/Fas-L).

- Activation of vitamin D also occurs intracellularly by **1-alpha hydroxylase**, which is **expressed in pancreatic beta cells**.

- Vitamin D regulates **calbindin**, a Ca-binding protein, which **modulates insulin release via regulation of intracellular calcium**. Calbindin may also protect against apoptosis via its ability to buffer intracellular calcium.

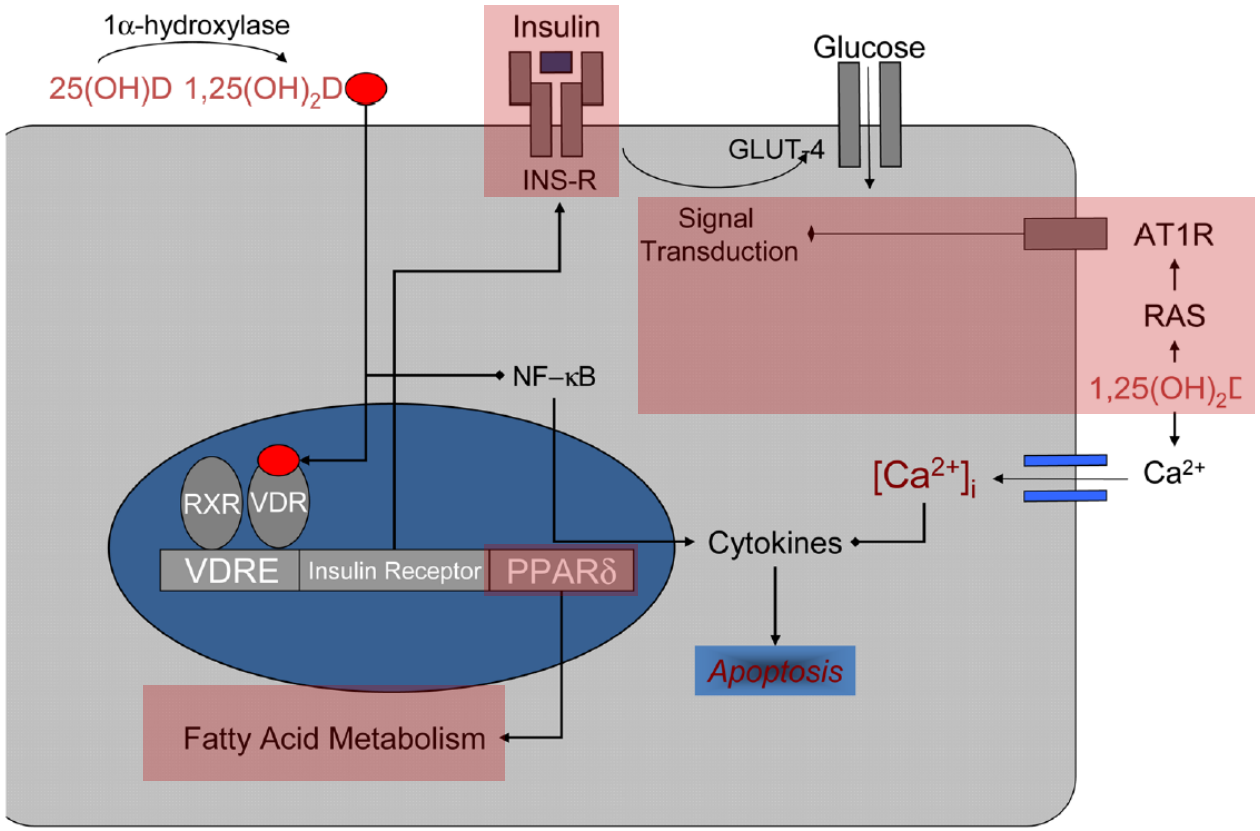


- Vitamin D may indirectly **regulates insulin secretion** via extracellular calcium (Ca2+) flux through the beta cell and intracellular calcium (Ca2+)

Mitri J and Pittas AG, Endocrinol Metab Clin North Am. 2014

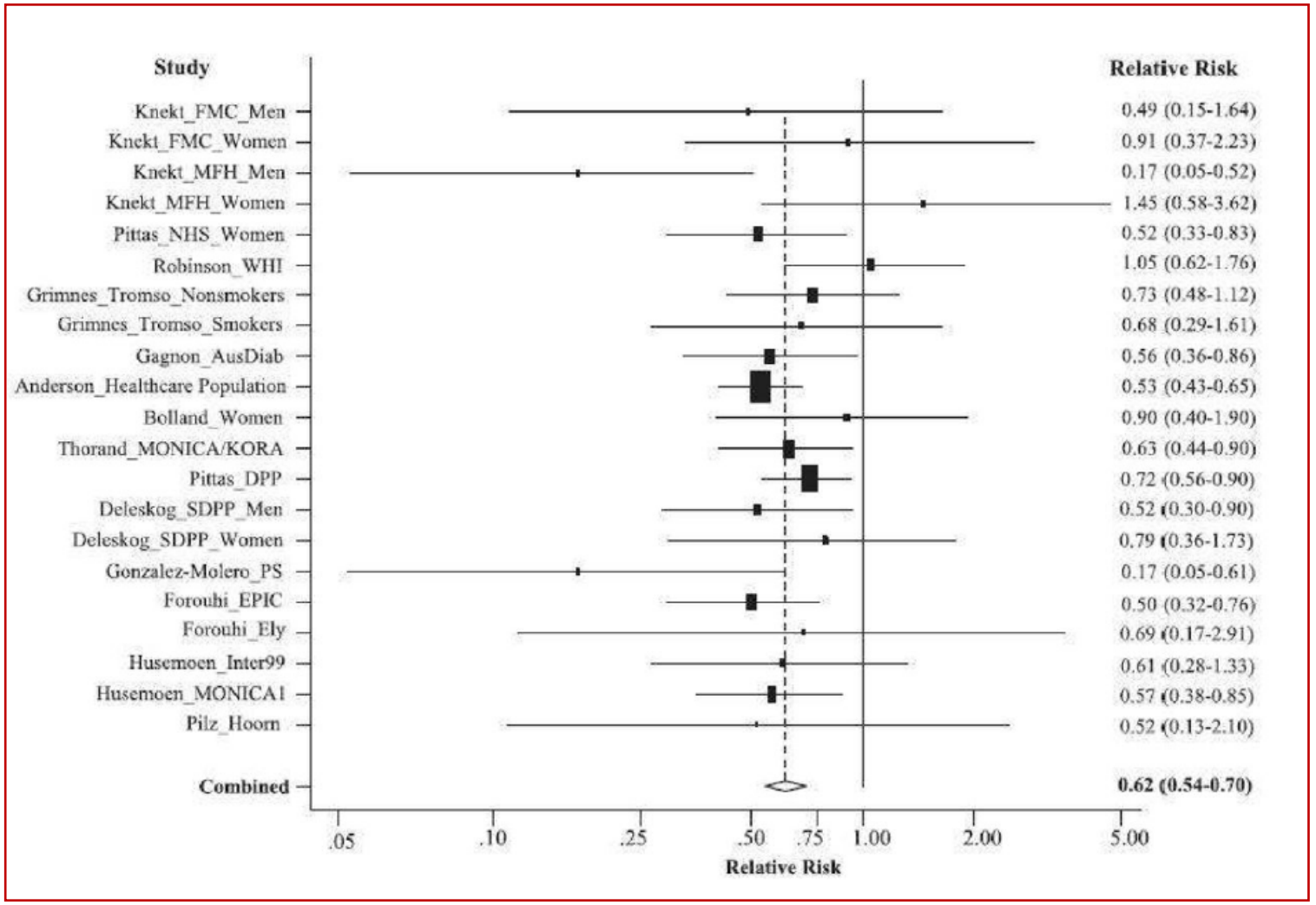
Vitamin D and insulin action in peripheral insulin target cells

- In **insulin target cells** (liver, adipose tissue and muscle) vitamin D **stimulates the expression of INS-R**
- VitD **activates PPAR-δ**, a transcription factor implicated in the regulation of fatty acid metabolism.
- VitD **regulates extracellular Ca and flux through cell membranes**. Changes in intracellular calcium contributes to insulin resistance *via* an impaired insulin signal transduction and a decreased glucose transporter activity.



Mitri J and Pittas AG, Endocrinol Metab Clin North Am. 2014

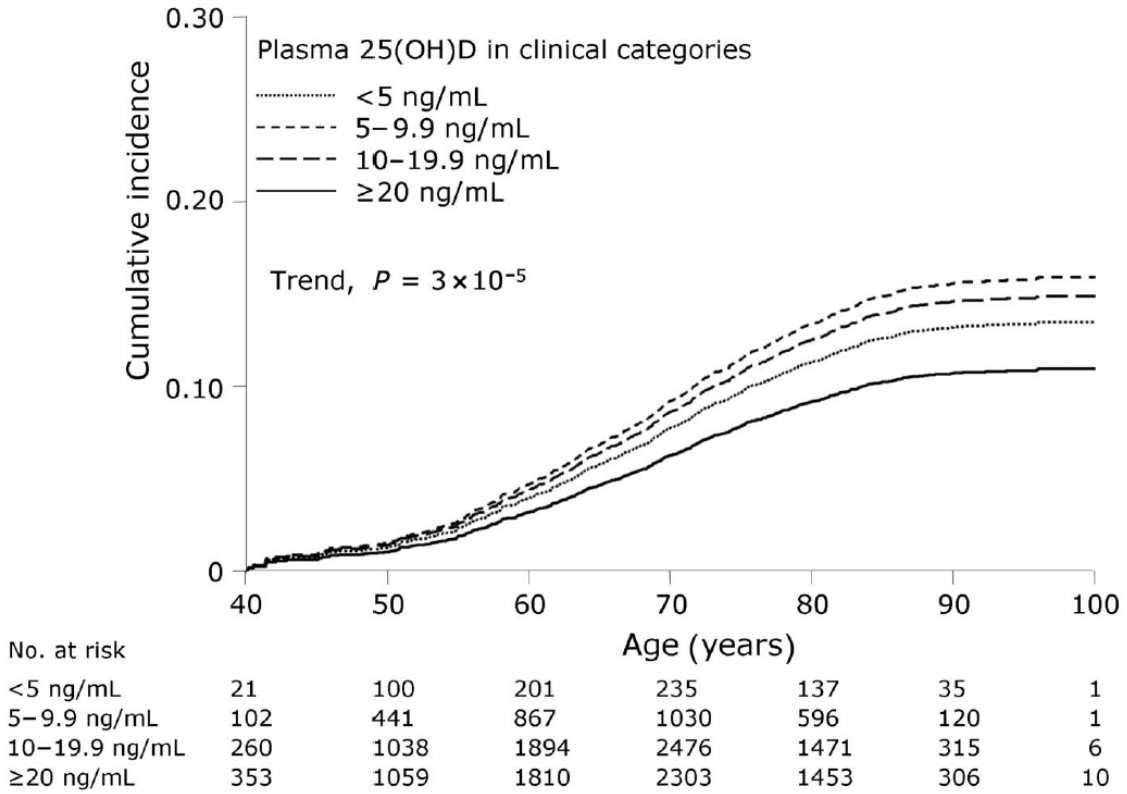
Risk of developing type 2 diabetes according to baseline vitamin D levels

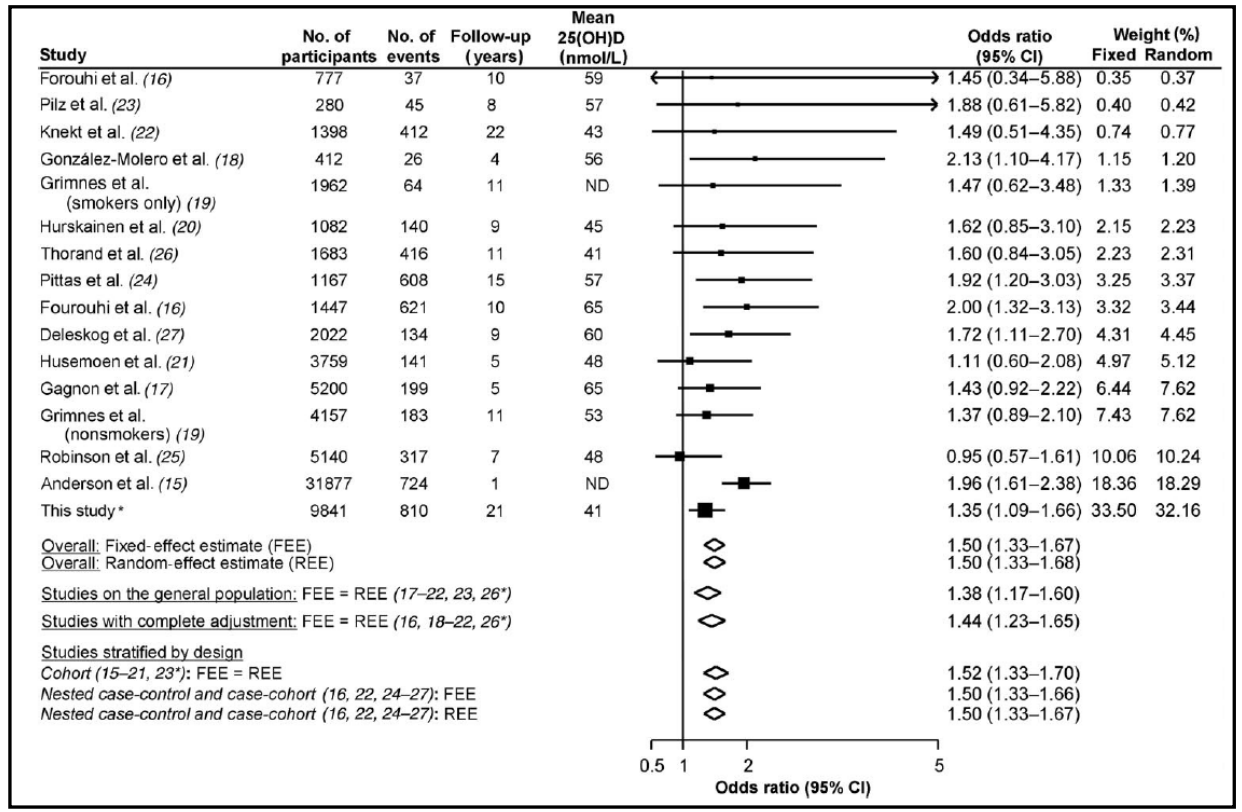


4 ng/ml increment in 25OHD levels is associated with a 4% lower risk of T2D

Song Y et al, Diabetes Care 2013

Low 25OHD and risk of type 2 diabetes: A prospective cohort study and metanalysis





Afzal S et al, Clin Chem. 2013

Vitamin D Supplementation in Diabetes

- Effects of vitamin D on glucose tolerance
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- **Vitamin D supplementation in diabetes**
  - Prevention of diabetes
  - Gluco-metabolic effects
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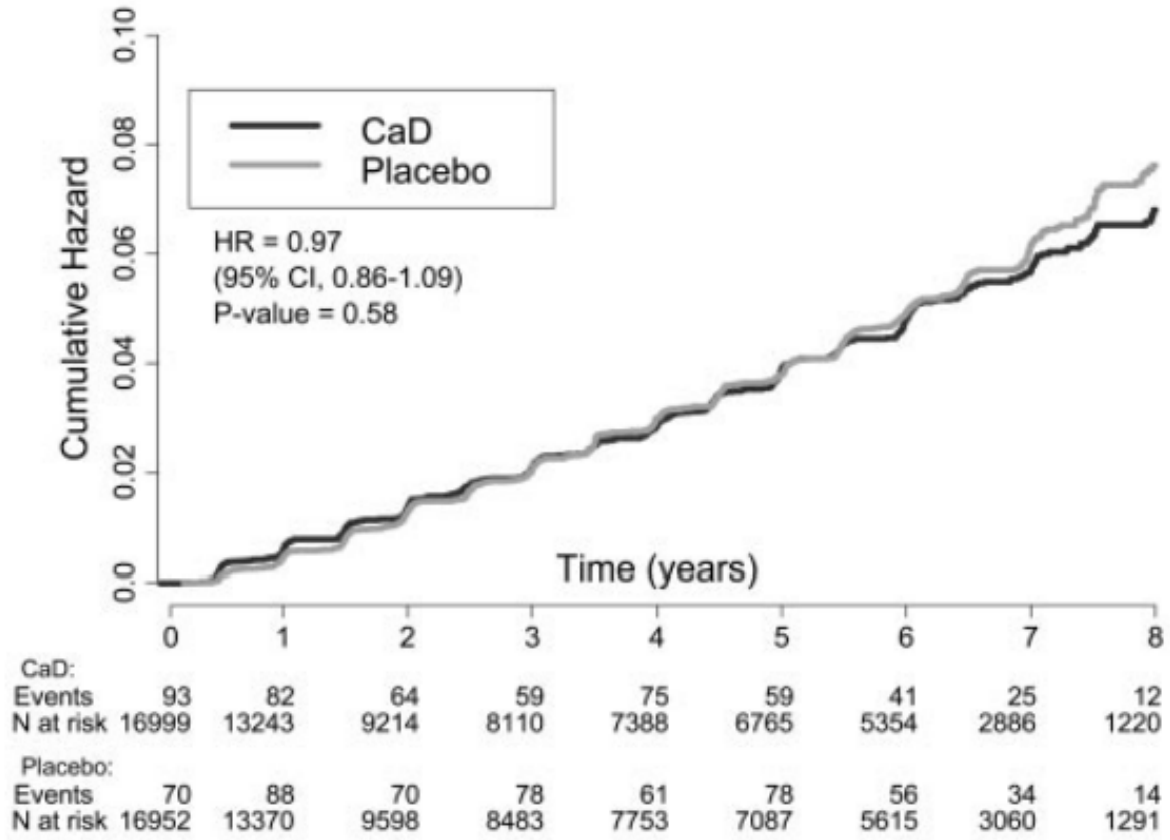
Calcium Plus Vitamin D Supplementation and the Risk of Incident Diabetes in the Women's Health Initiative



- N= 33,951 participants without self-reported diabetes at baseline
- Treatment: 1,000 mg elemental calcium plus 400 IU of vitamin D3 daily, or placebo

De Boer IH et al. Diabetes Care 31:701–707, 2008

Vitamin D Supplementation and Prevention of Type 2 Diabetes

Subgroup	Vitamin D	Placebo	Hazard Ratio for Diabetes (95% CI)
	no. of events/no. of participants		
Serum 25-hydroxyvitamin D			
<20 ng/ml	73/276	66/249	0.87 (0.61–1.22)
≥20 ng/ml	220/935	256/962	0.89 (0.74–1.06)
Race			
White	207/810	227/806	0.90 (0.75–1.09)
Black	64/301	69/315	0.83 (0.58–1.18)
Other	22/100	27/91	0.86 (0.48–1.56)
Glycemic criteria for prediabetes			
Met all three criteria	143/427	163/429	0.86 (0.68–1.09)
Met two criteria	150/784	160/783	0.90 (0.72–1.13)
Body–mass index			
<30	82/435	105/429	0.71 (0.53–0.95)
≥30	211/776	218/783	0.97 (0.80–1.17)
Impaired glucose tolerance			
Yes	191/604	215/635	0.92 (0.75–1.12)
No	102/607	108/577	0.86 (0.65–1.13)
Ethnic group			
Hispanic	36/120	27/105	1.14 (0.68–1.92)
Non–Hispanic	257/1091	296/1107	0.86 (0.72–1.02)
Sex			
Female	131/541	127/545	0.98 (0.77–1.26)
Male	162/670	196/667	0.82 (0.66–1.01)
Waist circumference			
<Median of 104.2 cm	127/620	135/585	0.82 (0.64–1.05)
≥Median of 104.2 cm	166/591	188/627	0.95 (0.76–1.17)
Age			
<Median of 60.9 yr	158/622	153/587	0.97 (0.77–1.21)
≥Median of 60.9 yr	135/589	170/625	0.80 (0.64–1.01)
Geographic location			
At or above 37° north latitude	205/892	235/898	0.85 (0.70–1.03)
Below 37° north latitude	88/319	88/314	0.97 (0.72–1.32)
Calcium intake from supplements			
No intake	198/826	216/793	0.81 (0.66–0.98)
Any intake	95/385	107/419	1.05 (0.79–1.40)

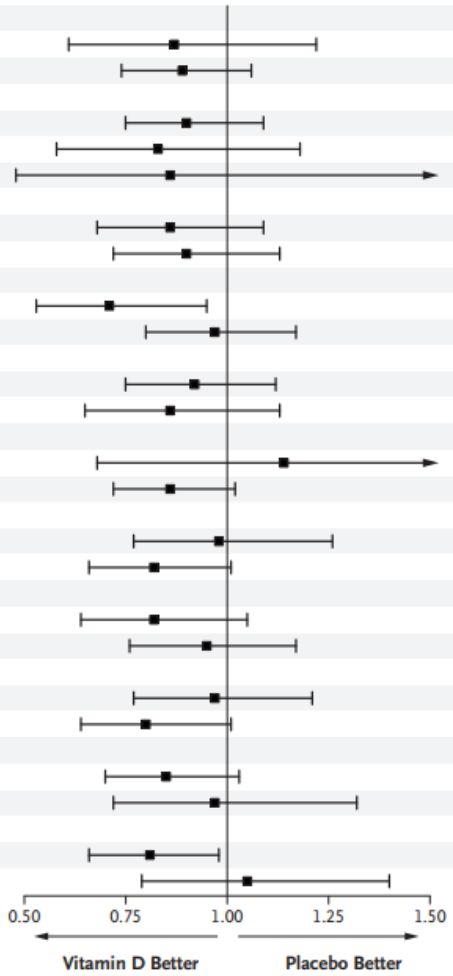
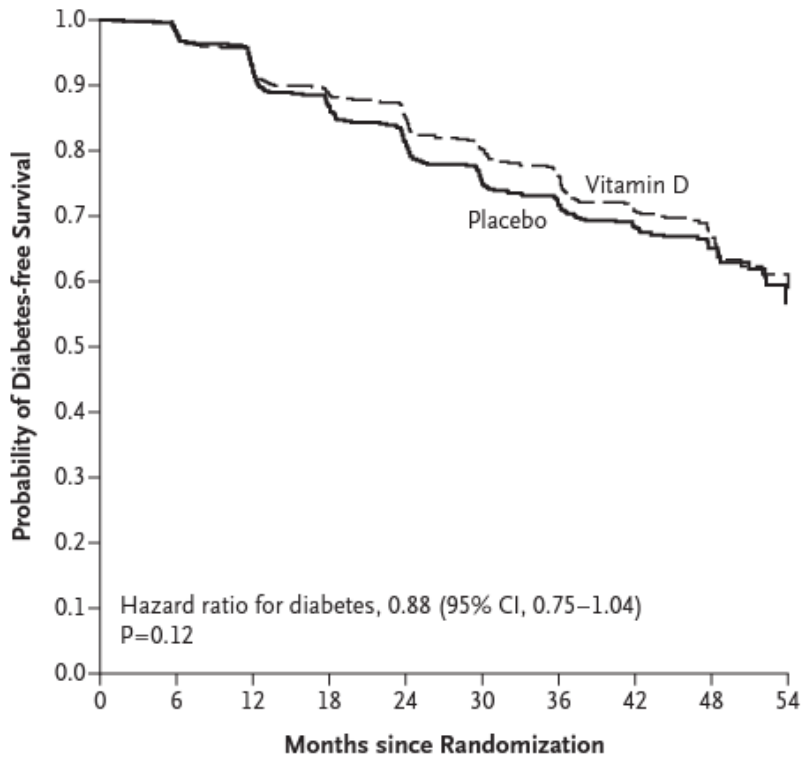


Figure 3. Prespecified Subgroup Analyses.

Participants met at least two of three glycemic criteria for prediabetes: fasting plasma glucose level, 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter); plasma glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) (impaired glucose tolerance); and glycated hemoglobin level, 5.7 to 6.4% (39 to 47 mmol per mole). To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.



No. at Risk

Vitamin D	1211	1171	1089	1001	812	625	466	283	141	21
Placebo	1212	1171	1091	975	779	577	419	258	121	13

Figure 2. Kaplan–Meier Curves for Survival Free from Diabetes among Adults at Risk for Type 2 Diabetes.

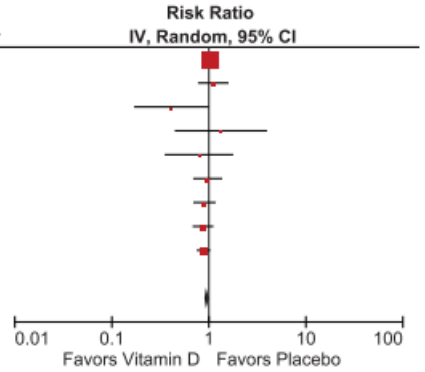
The hazard ratio for new-onset diabetes between the vitamin D group and the placebo group is derived from Cox regression, with stratification according to trial site, body-mass index, and race.

Pittas AG et al. N Engl J Med 2019;381:520-30

Effect of Vitamin D Supplementation on the Incidence of Diabetes

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
de Boer 2008	0.0121	0.0404	58.7%	1.01 [0.94, 1.10]	2008
Avenell 2009	0.1041	0.1854	3.6%	1.11 [0.77, 1.60]	2009
Dutta 2014	-0.8887	0.4528	0.6%	0.41 [0.17, 1.00]	2014
Davidson 2013	0.2852	0.5591	0.4%	1.33 [0.44, 3.98]	2015
Kuchay 2015	-0.2357	0.415	0.7%	0.79 [0.35, 1.78]	2015
Barengolts 2015	-0.029	0.1759	4.0%	0.97 [0.69, 1.37]	2015
Jorde 2016	-0.1054	0.1356	6.7%	0.90 [0.69, 1.17]	2016
Kawahara 2018	-0.1393	0.1257	7.7%	0.87 [0.68, 1.11]	2018
Pittas 2019	-0.1278	0.0816	17.6%	0.88 [0.75, 1.03]	2019
Total (95% CI)			**100.0%**	**0.96 [0.90, 1.03]**	

Heterogeneity: Tau² = 0.00; Chi² = 8.27, df = 8 (P = 0.41); I² = 3%
Test for overall effect: Z = 1.03 (P = 0.30)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Vitamin D dose >= 1000 IU/day					
Dutta 2014	-0.8887	0.4528	0.6%	0.41 [0.17, 1.00]	2014
Davidson 2013	0.2852	0.5591	0.4%	1.33 [0.44, 3.98]	2015
Barengolts 2015	-0.029	0.1759	4.0%	0.97 [0.69, 1.37]	2015
Kuchay 2015	-0.2357	0.415	0.7%	0.79 [0.35, 1.78]	2015
Jorde 2016	-0.1054	0.1356	6.7%	0.90 [0.69, 1.17]	2016
Kawahara 2018	-0.1393	0.1257	7.7%	0.87 [0.68, 1.11]	2018
Pittas 2019	-0.1278	0.0816	17.6%	0.88 [0.75, 1.03]	2019
Subtotal (95% CI)			**37.7%**	**0.88 [0.79, 0.99]**	

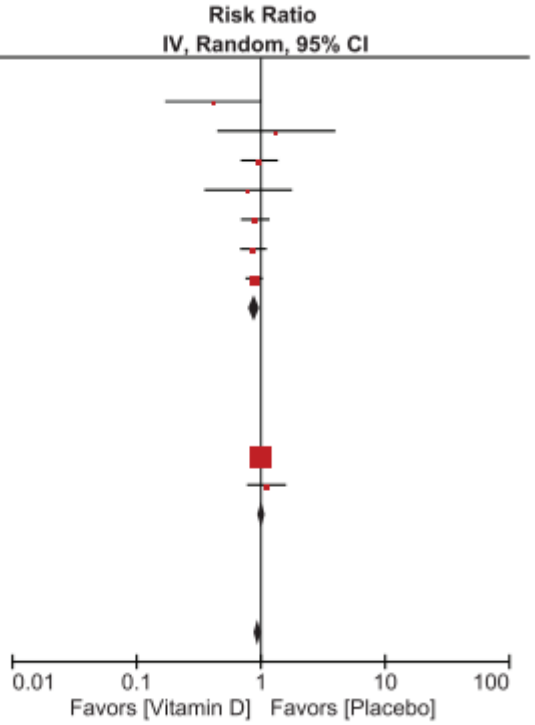
Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 6 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

Vitamin D dose < 1000 IU/day					
de Boer 2008	0.0121	0.0404	58.7%	1.01 [0.94, 1.10]	2008
Avenell 2009	0.1041	0.1854	3.6%	1.11 [0.77, 1.60]	2009
Subtotal (95% CI)			**62.3%**	**1.02 [0.94, 1.10]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)

Total (95% CI)			**100.0%**	**0.96 [0.90, 1.03]**	

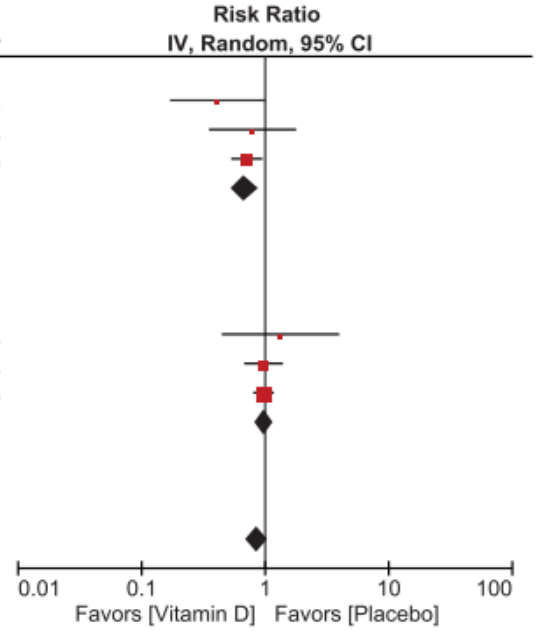
Heterogeneity: Tau² = 0.00; Chi² = 8.27, df = 8 (P = 0.41); I² = 3%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Chi² = 4.25, df = 1 (P = 0.04), I² = 76.5%



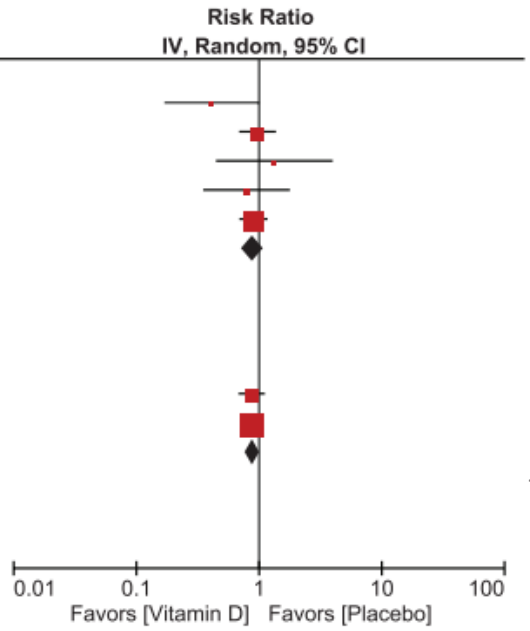
Conclusion:
vitamin D supplementation at moderate to high doses (≥1000 IU/day), significantly reduced the incidence risk of T2DM, compared with placebo

Barbarawi M et al.
J Clin Endocrinol Metab 2020;105: 2857–2868

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
BMI < 30					
Dutta 2014	-0.8887	0.4528	4.5%	0.41 [0.17, 1.00]	2014
Kuchay 2015	-0.2357	0.415	5.3%	0.79 [0.35, 1.78]	2015
Pittas 2019	-0.3425	0.1492	26.6%	0.71 [0.53, 0.95]	2019
Subtotal (95% CI)			**36.4%**	**0.68 [0.53, 0.89]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 2 (P = 0.49); I² = 0%					
Test for overall effect: Z = 2.83 (P = 0.005)					
BMI >=30					
Davidson 2013	0.2852	0.5591	3.0%	1.33 [0.44, 3.98]	2015
Barengolts 2015	-0.0305	0.1847	20.2%	0.97 [0.68, 1.39]	2015
Pittas 2019	-0.0305	0.0983	40.4%	0.97 [0.80, 1.18]	2019
Subtotal (95% CI)			**63.6%**	**0.98 [0.83, 1.16]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)			**100.0%**	**0.86 [0.71, 1.04]**	
Heterogeneity: Tau² = 0.01; Chi² = 6.76, df = 5 (P = 0.24); I² = 26%					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Chi² = 5.01, df = 1 (P = 0.03), I² = 80.0%					



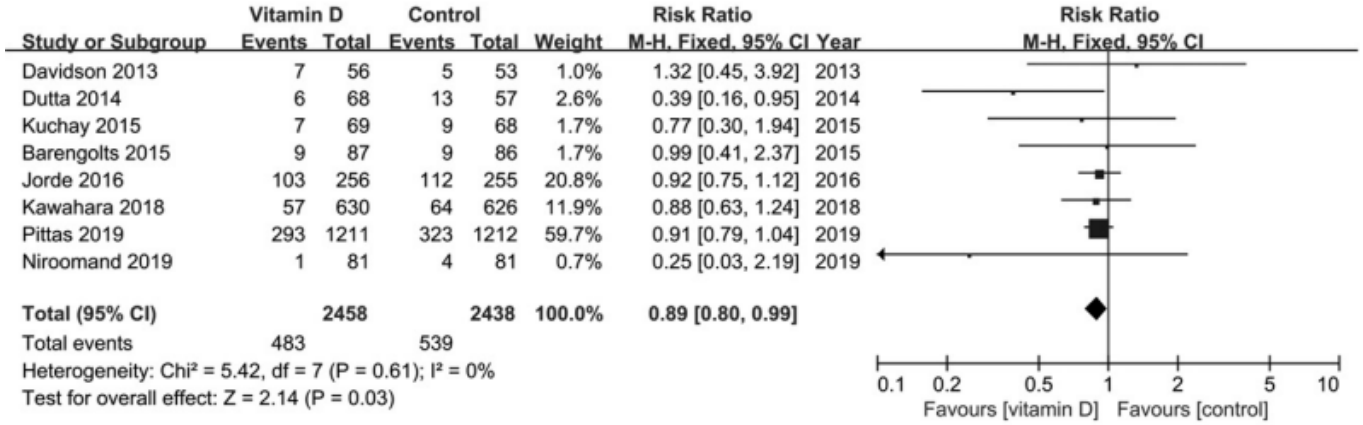
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Incidence of diabetes with loading vitamin D					
Dutta 2014	-0.8887	0.4528	4.8%	0.41 [0.17, 1.00]	2014
Barengolts 2015	-0.029	0.1759	32.1%	0.97 [0.69, 1.37]	2015
Davidson 2013	0.2852	0.5591	3.2%	1.33 [0.44, 3.98]	2015
Kuchay 2015	-0.2357	0.415	5.8%	0.79 [0.35, 1.78]	2015
Jorde 2016	-0.1054	0.1356	54.1%	0.90 [0.69, 1.17]	2016
Subtotal (95% CI)			**100.0%**	**0.89 [0.73, 1.08]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 4 (P = 0.44); I² = 0%					
Test for overall effect: Z = 1.14 (P = 0.25)					
Incidence of diabetes with daily Vitamin D					
Kawahara 2018	-0.1393	0.1257	29.6%	0.87 [0.68, 1.11]	2018
Pittas 2019	-0.1278	0.0816	70.4%	0.88 [0.75, 1.03]	2019
Subtotal (95% CI)			**100.0%**	**0.88 [0.77, 1.00]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%					
Test for overall effect: Z = 1.92 (P = 0.06)					



Barbarawi M et al.
J Clin Endocrinol Metab 2020;105: 2857–2868

Effects of Vitamin D Supplementation on Prevention of Type 2 Diabetes in Patients With Prediabetes: A Systematic Review and Meta-analysis

Risk of developing diabetes



Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Davidson 2013	7	56	5	53	1.0%	1.32 [0.45, 3.92]	2013
Dutta 2014	6	68	13	57	2.6%	0.39 [0.16, 0.95]	2014
Kuchay 2015	7	69	9	68	1.7%	0.77 [0.30, 1.94]	2015
Barengolts 2015	9	87	9	86	1.7%	0.99 [0.41, 2.37]	2015
Jorde 2016	103	256	112	255	20.8%	0.92 [0.75, 1.12]	2016
Kawahara 2018	57	630	64	626	11.9%	0.88 [0.63, 1.24]	2018
Pittas 2019	293	1211	323	1212	59.7%	0.91 [0.79, 1.04]	2019
Niroomand 2019	1	81	4	81	0.7%	0.25 [0.03, 2.19]	2019
Total (95% CI)		**2458**		**2438**	**100.0%**	**0.89 [0.80, 0.99]**	
Total events	483		539				

Heterogeneity: Chi² = 5.42, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Reversion of prediabetes to normal

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Davidson 2013	23	56	20	53	26.9%	1.09 [0.68, 1.74]	2013
Dutta 2014	23	68	10	57	14.2%	1.93 [1.00, 3.71]	2014
Barengolts 2015	8	87	6	86	7.9%	1.32 [0.48, 3.64]	2015
Jorde 2016	45	256	28	255	36.7%	1.60 [1.03, 2.48]	2016
Niroomand 2019	17	81	11	81	14.4%	1.55 [0.77, 3.09]	2019
Total (95% CI)		**548**		**532**	**100.0%**	**1.48 [1.14, 1.92]**	
Total events	116		75				

Heterogeneity: χ^2 = 2.48, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.97 (P = 0.003)

Conclusions:

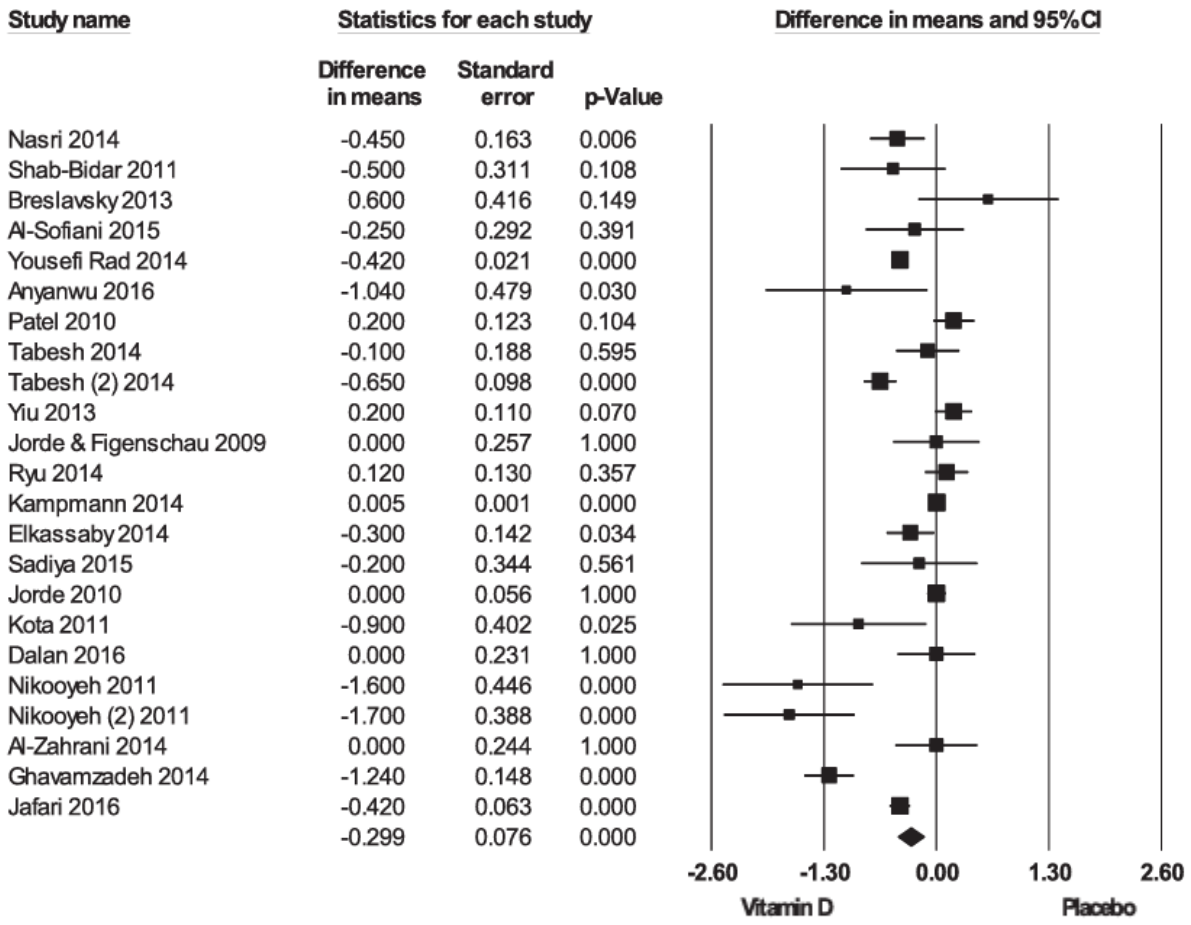
In persons with prediabetes, vitamin D supplementation **reduces the risk of T2DM** and **increases the reversion rate of prediabetes to normoglycemia**. The benefit of the prevention of T2DM could be limited to nonobese subjects.

Individual participant data meta-analyses are needed to confirm these findings.

Zhang Y et al. Diabetes Care 2020;43:1650–1658

The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

Mean difference in the change of HbA1c (%)



Subgroup Analysis	No. of Study	No. of Subjects: Vitamin D	No. of Subjects: Placebo	Mean Difference (95% CI)	*P* Value
Concomitant use of Ca					
HbA1c (%)					
D vs placebo	18	643	642	−0.25 ± 0.08 (−0.41 to −0.09)	0.003
D + Ca vs placebo	6	239	228	−0.50 ± 0.2 (−0.89 to −0.09)[a]	0.01
FPG (mg/dL)					
D vs placebo	16	598	596	−6.7 ± 2.2 (−11.0 to −2.2)	0.003
D + Ca vs placebo	6	239	228	−9.5 ± 4.9 (−18.9 to −0.2)[a]	0.04
HOMA-IR					
D vs placebo	8	212	208	−0.62 ± 0.3 (−1.2 to −0.05)	0.03
D + Ca vs placebo	4	174	163	−0.69 ± 0.3 (−1.34 to −0.04)	0.04
Obesity					
HbA1c (%)					
Obese	5	173	157	−0.16 ± 0.15 (−0.45 to 0.132)	0.2
Nonobese	19	709	713	−0.34 ± 0.08 (−0.51 to −0.18)[a]	< 0.001
FPG (mg/dL)					
Obese	5	173	157	−5.0 ± 1.8 (−8.6 to −1.3)	0.009
Nonobese	17	664	667	−8.1 ± 2.7 (−13.3 to −2.7)[a]	0.003
HOMA-IR					
Obese	3	104	92	−0.28 ± 0.16 (−0.60 to 0.04)	0.09
Nonobese	9	388	389	−0.74 ± 0.26 (−1.25 to −0.22)[a]	0.005
25(OH)D level at baseline					
HbA1c (%)					
<20 ng/mL	12	382	381	−0.29 ± 0.13 (−0.55 to −0.03)	0.02
≥20 ng/mL	12	500	489	−0.29 ± 0.09 (−0.46 to −0.12)	0.001
FPG (mg/dL)					
<20 ng/mL	11	367	365	−1.1 ± 1.4 (−4.0 to 1.6)	0.4
≥20 ng/mL	11	470	459	−8.6 ± 2.7 (−13.9 to −3.4)[a]	0.001
HOMA-IR					
<20 ng/mL	6	312	313	−0.43 ± 0.29 (−0.99 to 0.14)	0.1
≥20 ng/mL	6	180	168	−0.82 ± 0.32 (−1.44 to −0.20)[a]	0.01

Abbreviation: Ca, calcium.

[a]Significant difference between groups (t-test, $P < 0.05$).

Mirhosseini N et al. J Clin Endocrinol Metab 102: 3097–3110, 2017

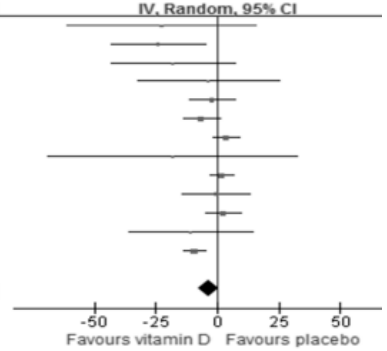
The Effect of Vitamin D Supplementation on Glycemic Control in Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis

fasting blood glucose

(B)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anyanwu 2016	-18.5	47.2	17	4.1	63.8	16	1.2%	-22.60 [-61.08, 15.88]
Baziar 2014	-15.06	46.07	41	9.06	42.25	40	4.0%	-24.12 [-43.36, -4.88]
Eftekhari 2011	-2	52	35	16	55.7	35	2.6%	-18.00 [-43.24, 7.24]
Jorde 2009	3.6	55.8	16	7.2	18	16	2.0%	-3.60 [-32.33, 25.13]
Kampmann 2014	1.98	7.2	7	4.14	10.8	8	10.2%	-2.16 [-11.35, 7.03]
Kim 2014	-1.27	10.96	15	5.23	9.75	15	12.1%	-6.50 [-13.92, 0.92]
Krul-Poel 2015	7.2	22.5	129	3.6	20.8	132	14.7%	3.60 [-1.66, 8.86]
Maggi 2014	-18	82.5	14	0	54	16	0.7%	-18.00 [-68.67, 32.67]
Punthakee 2012	-5.4	40.8	607	-7.2	39.7	614	15.6%	1.80 [-2.72, 6.32]
Ryu 2014 a	3.2	27.5	32	3.9	28.2	30	6.4%	-0.70 [-14.58, 13.18]
Ryu 2014 b	-0.9	21.8	64	-3.2	20.3	65	12.3%	2.30 [-4.97, 9.57]
Sadiya 2015	3.6	51.3	43	14.4	62.6	39	2.6%	-10.80 [-35.72, 14.12]
Yousefi 2014	0.67	10.14	28	10.04	7.59	30	15.5%	-9.37 [-14.00, -4.74]
Total (95% CI)			**1048**			**1056**	**100.0%**	**-3.59 [-7.94, 0.76]**

Heterogeneity: Tau² = 26.28; Chi² = 28.07, df = 12 (P = 0.005); I² = 57%
Test for overall effect: Z = 1.62 (P = 0.11)

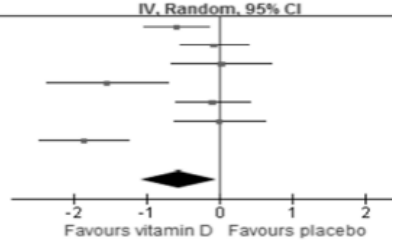


HOMA

(D)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baziar 2014	-1	2.26	41	0.43	2.52	40	15.6%	-0.59 [-1.04, -0.15]
Eftekhari 2011	1.22	2.6	35	1.41	2.1	35	15.4%	-0.08 [-0.55, 0.39]
Jorde 2009	0.3	23.5	16	-0.2	13.7	16	13.5%	0.03 [-0.67, 0.72]
Kim 2014	-0.12	0.36	15	0.46	0.37	15	12.2%	-1.55 [-2.38, -0.72]
Tabesh 2014	-0.02	0.17	29	-0.003	0.17	30	15.1%	-0.10 [-0.61, 0.41]
Witham 2010	4.2	13.6	19	4.2	16.7	21	14.1%	0.00 [-0.62, 0.62]
Yousefi 2014	-0.12	0.19	28	0.23	0.18	30	14.1%	-1.87 [-2.49, -1.24]
Total (95% CI)			**183**			**187**	**100.0%**	**-0.57 [-1.09, -0.04]**

Heterogeneity: Tau² = 0.41; Chi² = 34.87, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.12 (P = 0.03)

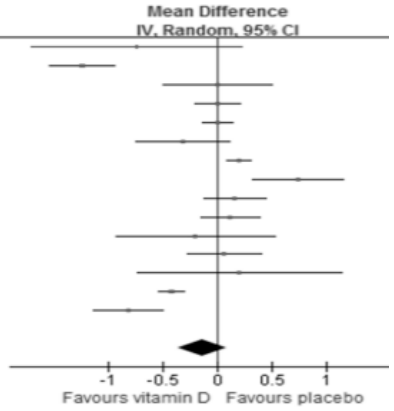


hemoglobin A1c

(C)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eftekhari 2011	0.82	1.9	35	1.56	2.2	35	3.3%	-0.74 [-1.70, 0.22]
Ghavamzadeh 2014	-0.18	0.45	26	1.06	0.62	25	7.4%	-1.24 [-1.54, -0.94]
Jorde 2009	-0.2	0.9	16	-0.2	0.5	16	6.0%	0.00 [-0.50, 0.50]
Kampmann 2014	0	0.2	7	0	0.2	8	8.0%	0.00 [-0.20, 0.20]
Krul-Poel 2015	0	0.6	129	0	0.6	132	8.2%	0.00 [-0.15, 0.15]
Nasri 2014	-0.03	0.47	30	0.29	1.11	30	6.5%	-0.32 [-0.75, 0.11]
Punthakee 2012	-0.2	1	607	-0.4	1	614	8.4%	0.20 [0.09, 0.31]
Rashidi 2016	-0.01	0.99	48	-0.75	1.08	46	6.6%	0.74 [0.32, 1.16]
Ryu 2014 a	0.06	0.57	32	-0.1	0.58	30	7.5%	0.16 [-0.13, 0.45]
Ryu 2014 b	0.1	0.8	64	-0.02	0.77	65	7.6%	0.12 [-0.15, 0.39]
Sadiya 2015	-0.2	1.4	43	0	1.9	39	4.5%	-0.20 [-0.93, 0.53]
Sugden 2008	0.01	0.6	17	-0.05	0.39	17	7.1%	0.06 [-0.28, 0.40]
Witham 2010	-0.1	1.6	19	-0.3	1.4	21	3.4%	0.20 [-0.74, 1.14]
Yousefi 2014	-0.53	0.2	28	-0.11	0.26	30	8.3%	-0.42 [-0.54, -0.30]
Zhou 2015	-1.43	0.58	31	-0.61	0.7	31	7.3%	-0.82 [-1.14, -0.50]
Total (95% CI)			**1132**			**1139**	**100.0%**	**-0.14 [-0.37, 0.08]**

Heterogeneity: Tau² = 0.15; Chi² = 158.85, df = 14 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.25 (P = 0.21)

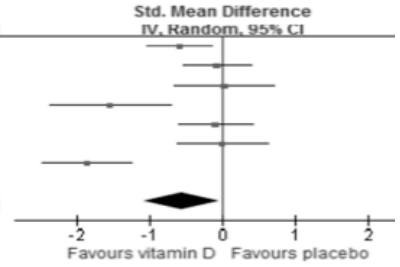


fasting insulin

(E)

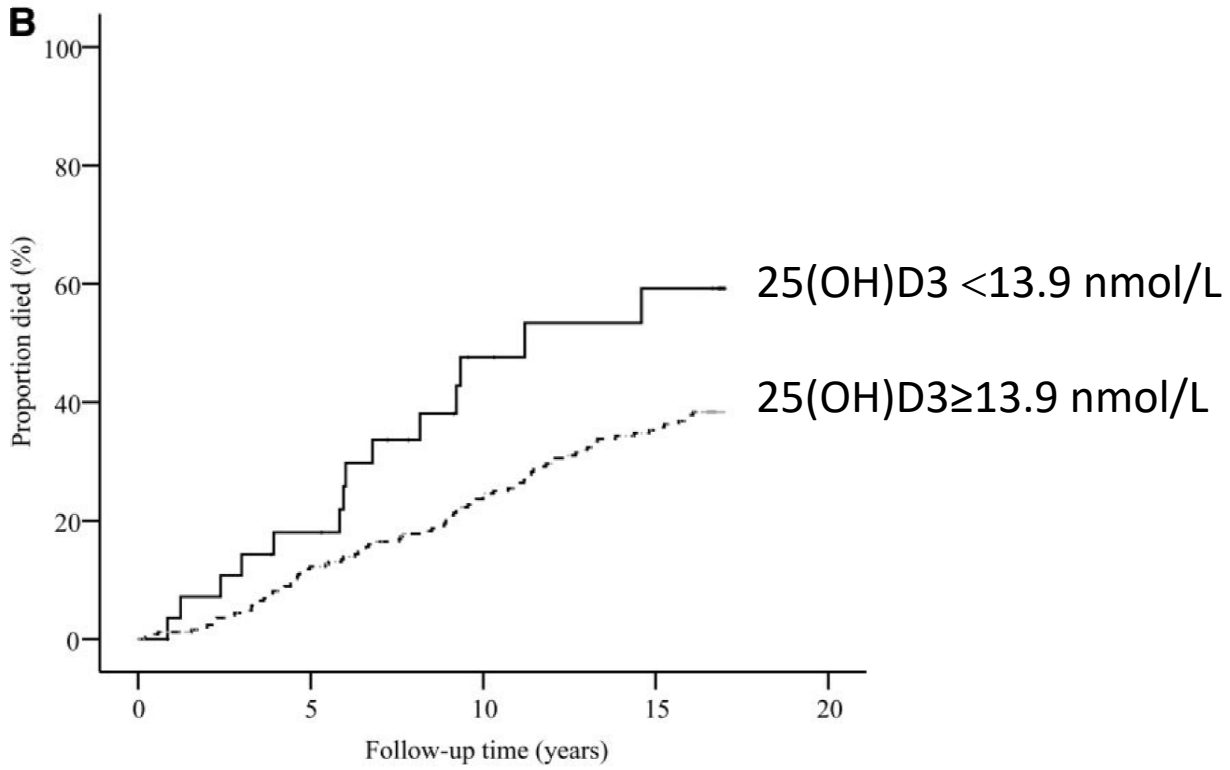
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baziar 2014	-1	2.26	41	0.43	2.52	40	15.6%	-0.59 [-1.04, -0.15]
Eftekhari 2011	1.22	2.6	35	1.41	2.1	35	15.4%	-0.08 [-0.55, 0.39]
Jorde 2009	0.3	23.5	16	-0.2	13.7	16	13.5%	0.03 [-0.67, 0.72]
Kim 2014	-0.12	0.36	15	0.46	0.37	15	12.2%	-1.55 [-2.38, -0.72]
Tabesh 2014	-0.02	0.17	29	-0.003	0.17	30	15.1%	-0.10 [-0.61, 0.41]
Witham 2010	4.2	13.6	19	4.2	16.7	21	14.1%	0.00 [-0.62, 0.62]
Yousefi 2014	-0.12	0.19	28	0.23	0.18	30	14.1%	-1.87 [-2.49, -1.24]
Total (95% CI)			**183**			**187**	**100.0%**	**-0.57 [-1.09, -0.04]**

Heterogeneity: Tau² = 0.41; Chi² = 34.87, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.12 (P = 0.03)



Li X et al. Nutrients 2018, 10, 375; doi:10.3390/nu10030375

VITAMIN D AND CARDIOVASCULAR DISEASE IN DIABETES



- In T2D patients, **severe vitamin D deficiency predicts increased risk of cardiovascular mortality**, independent of conventional cardiovascular risk factors. Whether vitamin D substitution improves prognosis remains to be investigated.

Joergensen C et al , Diabetes Care, 2010

Rev Endocr Metab Disord
DOI 10.1007/s11154-016-9403-y

Vitamin D and diabetes mellitus: Causal or casual association?

M. Grammatiki[1] · E. Rapti[1] · S. Karras[1] · R. A. Ajjan[2] · Kalliopi Kotsa[1,3]

Abstract The incidence of both type 2 and type 1 diabetes mellitus has been increasing worldwide. Vitamin D deficiency, or the awareness of its prevalence, has also been increasing. Vitamin D may have a role in the pathogenic mechanisms predisposing to type 2 diabetes by modulating insulin resistance and/or pancreatic β-cell function. Vitamin D status or elements involved in its activation or transport may also be involved in the development of type 1 diabetes mellitus through immunomodulatory role . Based on these observations a potential association between vitamin D and diabetes has been hypothesized. In this review we discuss up to date evidence linking vitamin D with the development of diabetes. Moreover, the role of vitamin D supplementation in the prevention of both types of diabetes is analysed together with its role in improving glycemic control in diabetic patients. We also address the potential role of vitamin D deficiency in the development of macro- and microvascular complications in diabetes. Finally, we provide recommendation for Vitamin D therapy in diabetes in view of current evidence and highlight areas for potential future research in this area.

Keywords Vitamin D · 25-hydroxyvitamin D · Diabetes mellitus · Type 1 diabetes · Type 2 diabetes · Diabetes complications

Abbreviations

T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
VDR	Vitamin D receptor
PTH	Parathyroid hormone
GLUT-4	Glucose transporter-4
PPAR	Peroxisome proliferator-activated receptor
25(OH)D	25-hydroxyvitamin D
OGTT	Oral glucose tolerance test
HbA1c	Glycated hemoglobin
VDBP	Vitamin D binding protein
NOD mice	Non obese diabetic mice
CRF	Chronic renal failure
RAAS	Rennin-angiotensin-aldosterone system
GFR	Glomerular filtration rate
DN	Diabetic neuropathy
DR	Diabetic retinopathy
CHD	Coronary heart disease
CVD	Cardiovascular disease
IMT	Intima-media thickness

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Published online: 07 January 2017

1 Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition of multifactorial nature with insulin resistance, and subsequent pancreatic beta cell failure, playing a key role in pathogenesis [1]. In contrast, type 1 diabetes mellitus (T1DM) is the result of a progressive autoimmune destruction of pancreatic beta cells in genetically susceptible individuals [2, 3]. Vitamin D,

Table 4 Vitamin D and diabetes complications: A resume

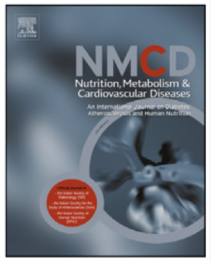
Microvascular Complications
Diabetic Renal Disease
Higher risk of diabetic nephropathy in vitamin D-deficient patients.
Vitamin D therapy reduces urinary albumin secretion in diabetes patients.
In need of further supplementation studies.
Diabetic neuropathy
Oral supplementation improves neuropathic symptoms.
Careful vitamin D supplementation monitoring is needed.
Data in T1DM patients are scarce.
Diabetic retinopathy
Higher risk of diabetic retinopathy in vitamin D-deficient T1DM patients.
VDR gene polymorphisms may be linked to retinopathy risk in T1DM.
Data in T2DM patients are scarce.
Vitamin D supplementation in vitamin D deficient T1DM and T2DM seems rational.
Macrovascular Complications
25(OH)D levels are an independent predictor of incident macrovascular events among T2DM patients.
No association of 25(OH)D levels with the prevalence of CVD among T1DM patienst has been proven yet.

Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 2210–2233

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



Management of bone fragility in type 2 diabetes: Perspective from an interdisciplinary expert panel

Iacopo Chiodini [a,b,1], Agostino Gaudio [c,1], Andrea Palermo [d], Nicola Napoli [d], Fabio Vescini [e], Alberto Falchetti [a,f], Daniela Merlotti [g,h], Cristina Eller-Vainicher [i], Vincenzo Carnevale [j], Alfredo Scillitani [k], Giuseppe Pugliese [l], Domenico Rendina [m], Antonio Salcuni [n], Francesco Bertoldo [o], Stefano Gonnelli [g], Ranuccio Nuti [g], Vincenzo Toscano [p], Vincenzo Triggiani [q], Simone Cenci [h], Luigi Gennari [g,*]

Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 2210–2233

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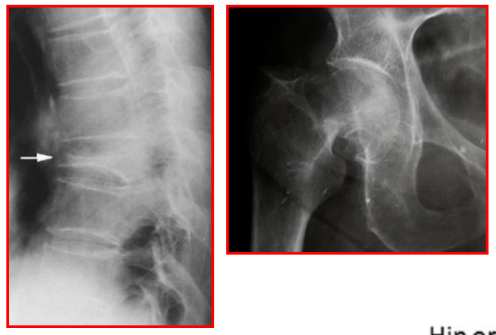
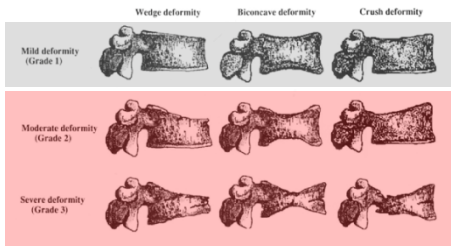
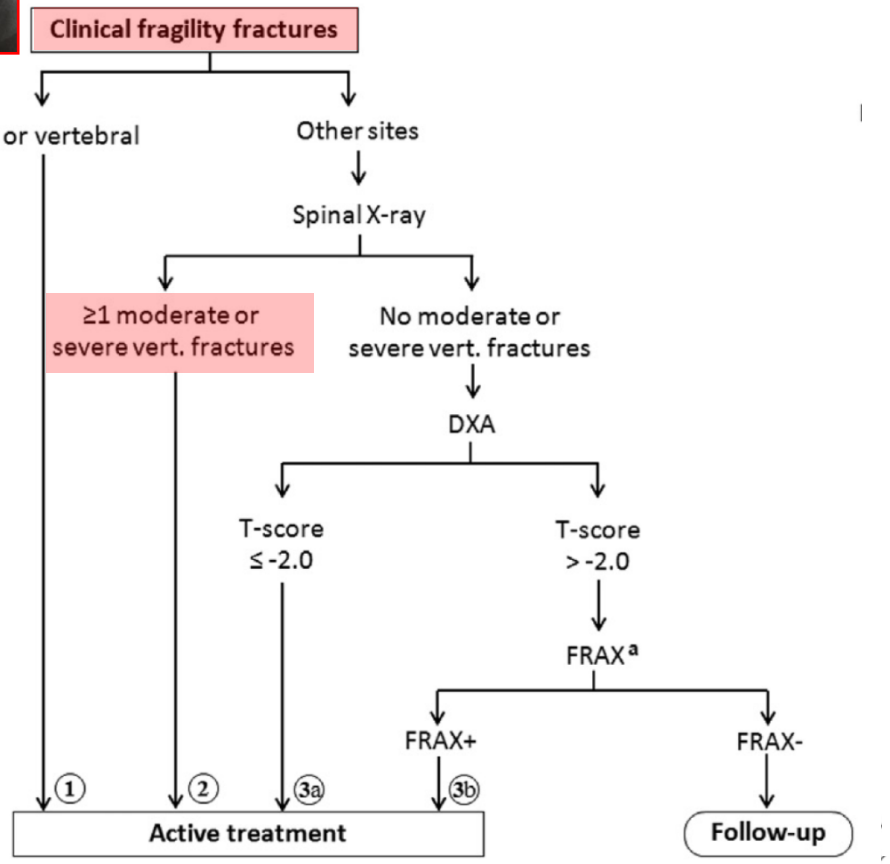
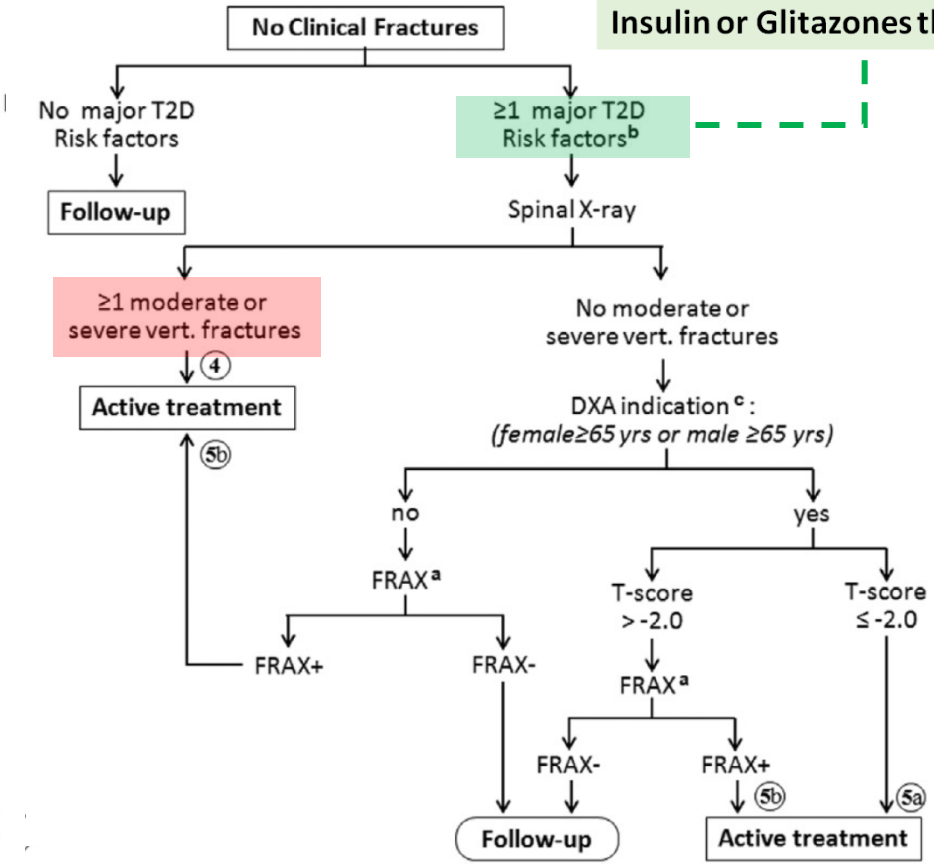


Management of bone fragility in type 2 diabetes: Perspective from an interdisciplinary expert panel







RISK FACTORS
Long T2D duration (≥ 10yrs)
Chronic T2D complications (≥ 1)
Persistent HbA1c ≥ 8% (for ≥ 1 yr)
Insulin or Glitazones therapy

Chiodini I et al.
Nutr Metab Cardiovasc Dis. 2021;31(8):2210-2233

Management of bone fragility in type 2 diabetes: Perspective from an interdisciplinary expert panel

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Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Which are the risk factors for bone fragility in type 2 diabetes?

Falling history, sarcopenia, and vitamin D deficiency

Vitamin D deficiency might further increase fall risk and fracture risk in T2D, albeit an U-shaped association between vitamin D and falls has been suggested, with high, intermittent vitamin D doses being associated with increased risk of falling [50]. Moreover, vitamin D deficiency has been found to be more common in T2D subjects than in non-diabetic individuals [51] and circulating vitamin D levels in T2D patients have been inversely correlated with HbA1c levels, even after controlling for confounding factors, such as BMI and diabetes duration [52]. Low vitamin D levels (e.g., <20 ng/ml) have been associated with an increased risk of vertebral fractures in T2D men, but not women [53]. Thus, despite the possibility to improve metabolic control or to prevent the onset of the disease by vitamin D supplementation in T2D patients is still debated, correcting vitamin D deficiency/insufficiency should be advisable in most T2D patients [17].

How to prevent and treat bone fragility in T2D patients?

Dietary and lifestyle recommendations

glucose tolerance [169]. Based on the above considerations and given the lack of major safety and toxicity concerns about vitamin D supplementation, members of this panel suggest that, when possible, an adequate 25OHD threshold around 30 ng/dl should be pursued in T2D patients.

nutrients

MDPI

Review

Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Francesco Bertoldo [1], Luisella Cianferotti [2], Marco Di Monaco [3], Alberto Falchetti [4,*], Angelo Fassio [5], Davide Gatti [5], Luigi Gennari [6], Sandro Giannini [7], Giuseppe Girasole [8], Stefano Gonnelli [6], Nazzarena Malavolta [9], Salvatore Minisola [10], Mario Pedrazzoni [11], Domenico Rendina [12], Maurizio Rossini [5] and Iacopo Chiodini [13,14]

Table 1. Definition of Vitamin D Status.

	Deficiency *	Insufficiency *	Optimal * Optimum *
GENERAL POPULATION	<10 ng/mL	<20 ng/mL	**20–50 ng/mL**
POPULATION AT RISK ** OR ON TREATMENT WITH *BONE MODIFYING AGENTS*	<10 ng/mL	<30 ng/mL	**30–50 ng/mL**

* Reported cut-off values should be considered with a margin of variability of +/−10%, considering the analytical variability of the 25(OH)D dosage. Moreover, due to the seasonal variability of 25(OH)D levels, a dosage performed at the end of winter/early spring should be particularly considered. A serum value of <10 ng/mL (25 nmol/L) is associated with rickets and osteomalacia, if long lasting. From ng/mL to nmol/L: ng/mL × 2.5.
** The population at risk of hypovitaminosis is shown in Table 2.

Table 2. Population/condition at risk of hypovitaminosis D.

- Old people (≥75 years)
- Institutionalized subjects or conditions associated with inadequate solar exposure
- Obesity
- Pregnancy and breast-feeding
- Metabolic bone diseases and other skeletal disorders
- Vegan diet
- Anorexia nervosa
- Chronic renal failure
- Cancer (in particular breast, prostate, and colon)
- Type 2 diabetes mellitus
- Intestinal malabsorption and bariatric surgery
- Drugs that interfere with the absorption or hepatic metabolism of vitamin D (antiepileptics, glucocorticoids, antiviral AIDS, antifungal agents, cholestyramine)
- Cystic fibrosis

Bertoldo F et al. Nutrients 2022, 14, 4148. https://doi.org/10.3390/nu14194148

The association of serum 25-hydroxyvitamin D and vertebral fractures in patients with type 2 diabetes

Prevalence of vertebral fracture and severity according to vitamin D statusin men and women

	25(OH)D level [ng/mL]			*p* value
	≥ 30	20-29.9	< 20	
I. Men				
Presence of vertebral fracture	10 (9.4%)	5 (17.9%)	10 (21.7%)	0.036
Severity of vertebral fracture				0.092
Mild	2 (1.8%)	3 (10.7%)	4 (8.7%)	
Moderate	7 (6.6%)	2 (7.1%)	5 (10.9%)	
Severe	1 (0.9%)	0 (0%)	1 (2.2%)	
II. Women				
Presence of vertebral fracture	10 (14.4%)	9 (19.1%)	12 (26.6%)	0.111
Severity of vertebral fracture				0.410
Mild	0 (0%)	2 (4.3%)	6 (13.3%)	
Moderate	5 (7.2%)	3 (6.4%)	1(2.2%)	
Severe	5 (7.2%)	4 (8.5%)	5 (11.1%)	

Associations between vitamin D status and the presence of vertebral fractures in men and women

25(OH)D	Model 1	Model 2	Model 3
A. Men			
< 20 ng/mL	3.09* (1.15-8.29)	3.83*(1.12-13.19)	7.87*(1.69-36.71)
20–29.9 ng/mL	2.22 (0.67-7.31)	2.61 (0.63-10.77)	5.96 (0.93-38.16)
≥ 30 ng/mL	Reference group	Reference group	Reference group
B. Women			
< 20 ng/mL	2.28 (0.83-6.21)	3.03 (0.88-10.34)	3.40 (0.78-14.71)
20–29.9 ng/mL	1.27 (0.45-3.56)	1.16 (0.34-3.95)	1.12 (0.26-4.85)
≥ 30 ng/mL	Reference group	Reference group	Reference group

*$p < 0.05$ *vs.* reference group

Model 1: adjusted for age. Model 2: model 1 additionally adjusted for duration of diabetes, insulin use, use of thiazolidinedione, statin use, stroke, CAOD, presence of nephropathy, and neuropathy. Model 3: model 2 additionally adjusted for BMI, falling history, smoking, alcohol consumption, and regular walking.

Kim YJ, et al. Endocr J. 2013;60(2):179-84. doi: 10.1507/endocrj.ej12-0269.

SUMMARY and CONCLUSIONS

- **Vitamin D deficiency** may be **common in patients with diabetes**
- **Experimental studies** indicate a biologically plausible role of vitamin D on glucose metabolism (vitamin D may modulate insulin secretion and sensitivity)
- **Longitudinal observational studies** suggest that vitamin D levels are inversely associated with the incidence of diabetes in different populations, including populations with prediabetes
- Most **intervention clinical trials** are **inconclusive** for a role of vitamin D supplementation on diabetes prevalence (mostly performed in subjects with normal vitamin D levels)
- In diabetic patients vitamin D might improve glucose control and impact on the risk/outcome of major complications
- There is very **limited information** about the role of **vitamin D suplementation for skeletal health** in diabetic patients

ALIMENTAZIONE E VITAMINA D

Roma – Hotel Mediterraneo - 2 dicembre 2022

III° Modulo formativo

Modalità di supplementazione con vitamina D

La supplementazione di Vit. D nel paziente diabetico

Luigi Gennari

Dipartimento di scienze Mediche, Chirurgiche e Neuroscienze,
Università di Siena